

Attorney Docket No. PC10636A
Application No. 09/833,169

Amendments to the Claims

1. (previously presented) A method for treating sexual arousal disorder consisting of:

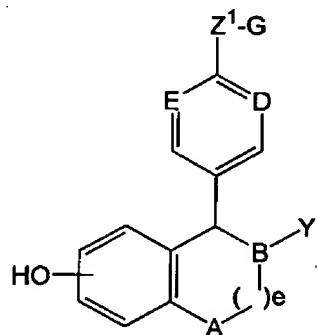
administering to a female subject in need thereof, an effective amount of an estrogen agonist / antagonist, and optionally,

co-administering an effective amount of a cyclic guanosine 3',5'-monophosphate elevator;

optionally with a pharmaceutically acceptable vehicle, carrier or diluent.

2. (Currently amended) A method for treating sexual arousal disorder consisting of comprising:

administering to a female subject in need thereof, an effective amount of an estrogen agonist/antagonist compound of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4 ;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4 ;

(c) $\text{C}_3\text{-C}_8$ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4 ;

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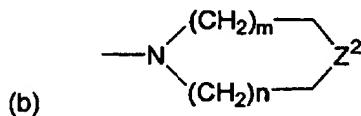
- (d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4 ;
- (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of $-O-$, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4 ;
- (f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of $-O-$, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4 ; or
- (g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of $-O-$, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4 ;

Z^1 is

- (a) $-(CH_2)_p W(CH_2)_q-$;
- (b) $-O(CH_2)_p CR^5R^8-$;
- (c) $-O(CH_2)_p W(CH_2)_q-$;
- (d) $-OCHR^2CHR^3-$; or
- (e) $-SCHR^2CHR^3-$;

G is

- (a) $-NR^7R^8-$;

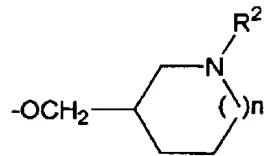


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is $-NH-$, $-O-$, $-S-$, or $-CH_2-$;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4 ; or

- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4 ; or

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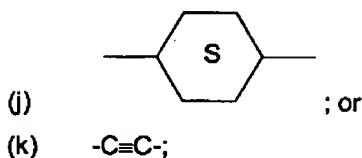


Z^1 and G in combination may be

W is

- (a) $-\text{CH}_2-$;
- (b) $-\text{CH}=\text{CH}-$;
- (c) $-\text{O}-$;
- (d) $-\text{NR}^2-$;
- (e) $-\text{S}(\text{O})_n-$;

- (f) $-\text{C}=\text{O}-$;
- (g) $-\text{CR}^2(\text{OH})-$;
- (h) $-\text{CONR}^2-$;
- (i) $-\text{NR}^2\text{CO}-$;



(j) $-\text{C}_6\text{H}_4-$; or

- (k) $-\text{C}\equiv\text{C}-$;

R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^2 and R^3 are independently

- (a) hydrogen; or
- (b) $\text{C}_1\text{-C}_4$ alkyl;

R^4 is

- (a) hydrogen;
- (b) halogen;
- (c) $\text{C}_1\text{-C}_6$ alkyl;
- (d) $\text{C}_1\text{-C}_4$ alkoxy;
- (e) $\text{C}_1\text{-C}_4$ acyloxy;
- (f) $\text{C}_1\text{-C}_4$ alkylthio;
- (g) $\text{C}_1\text{-C}_4$ alkylsulfinyl;
- (h) $\text{C}_1\text{-C}_4$ alkylsulfonyl;
- (i) hydroxy ($\text{C}_1\text{-C}_4$)alkyl;
- (j) aryl ($\text{C}_1\text{-C}_4$)alkyl;

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- (k) -CO₂H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO₂NHR;
- (o) -NH₂;
- (p) C₁-C₄ alkylamino;
- (q) C₁-C₄ dialkylamino;
- (r) -NHSO₂R;
- (s) -NO₂;
- (t) -aryl; or
- (u) -OH;

R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

R⁷ and R⁸ are independently

- (a) phenyl;
- (b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;
- (c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e) C₁-C₈ alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

n is 0, 1 or 2;

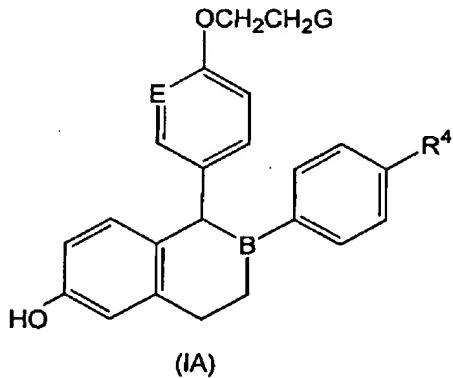
p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof, and optionally, co-administering an effective amount of a cyclic guanosine 3',5'-monophosphate elevator, optionally with a pharmaceutically acceptable vehicle, carrier or diluent.

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3. (Previously presented) The method of claim 2 wherein said estrogen agonist / antagonist is a compound of formula (IA):



wherein G is



R⁴ is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

4. (Currently amended) The method of claim 3 wherein said estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

5. (Currently amended) The method of claim 4 wherein said estrogen agonist / antagonist is in the form of a (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

Claims 6.-9. (canceled)

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10. (Previously presented) A method for treating sexual arousal disorder comprising:
administering to a female subject in need thereof, an effective amount of an estrogen agonist / antagonist, and further comprising co-administrering a cyclic guanosine 3',5'-monophosphate elevator.

11. (Previously presented) The method of claim 10 wherein said cyclic guanosine 3',5'-monophosphate elevator is a PDE_v phosphodiesterase inhibitor.

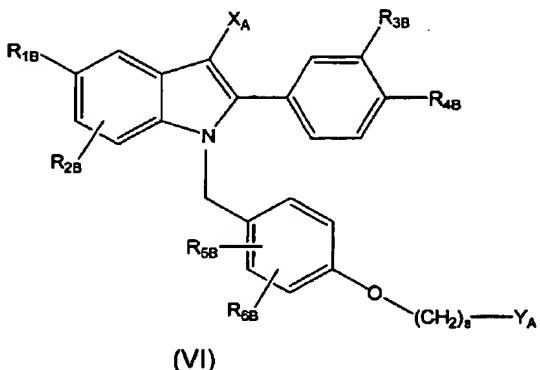
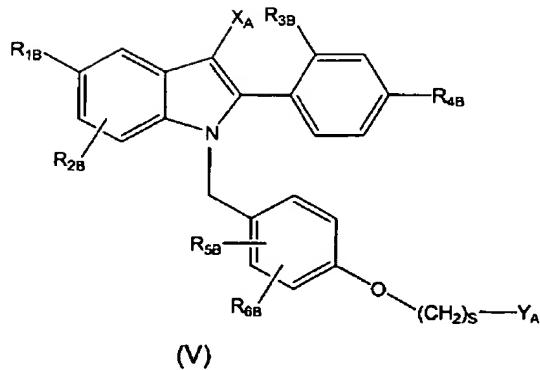
12. (Previously presented) The method of claim 11 wherein the PDE_v phosphodiesterase inhibitor is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxy-phenyl]sufonyl]-4-methylpiperazine citrate salt.

Claims 13.-39. (canceled)

40. (Currently amended) The method of claim 1 wherein said estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, raloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof.

41. (Previously presented) The method of claim 1 wherein said estrogen agonist / antagonist is a compound selected from the formulas V or VI:

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wherein:

R_{1B} is selected from H, OH, -O-C(O)-C₁-C₁₂ alkyl (straight chain or branched), -O-C₁-C₁₂ alkyl (straight chain or branched or cyclic), or halogens or C₁-C₄ halogenated ethers,

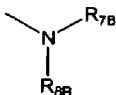
R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, -O-C(O)-C₁-C₁₂ (straight chain or branched), -O-C₁-C₁₂ (straight chain or branched or cyclic), halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₈ alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

X_A is selected from H, C₁-C₈ alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:

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wherein:

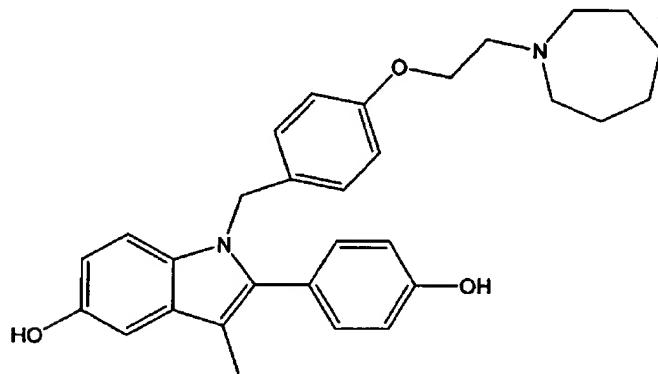
- a) R_{7B} and R_{8B} are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or
- b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen,

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hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

42. (Currently amended) The method of claim 41 wherein said estrogen agonist / antagonist is the compound, TSE-424, of formula Va below:

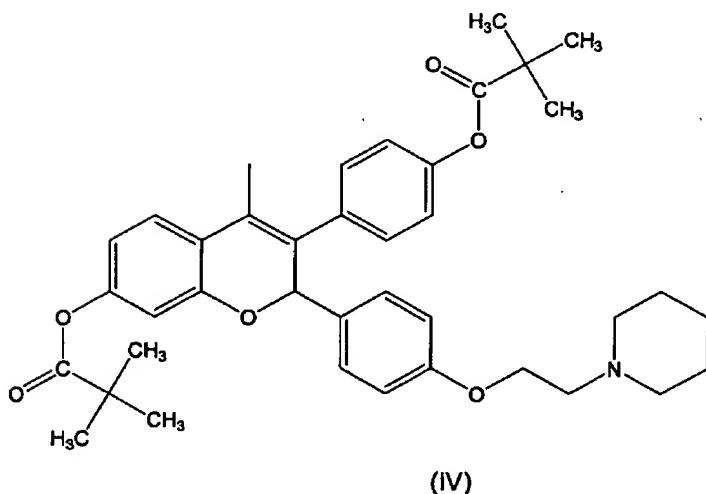
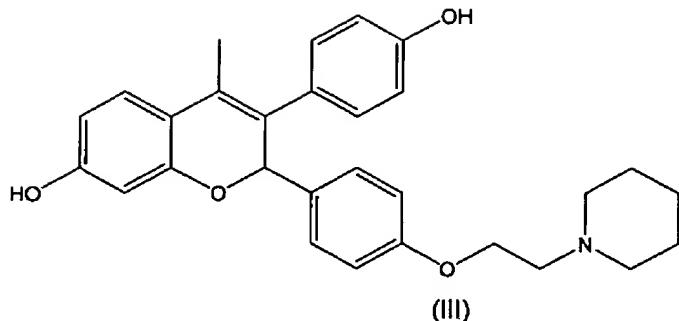


(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

43. (Currently amended) The method of claim 1 wherein said estrogen agonist / antagonist is EM-652 of formula III below or is EM-800 of formula IV below:

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er an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

44. (Currently amended) A method for treating sexual arousal disorder
comprising consisting of:

administering to a female subject in need thereof, an effective amount of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

45. (Currently amended) A method for treating sexual arousal disorder
comprising consisting of:

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administering to a female subject in need thereof, an effective amount of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

46. (Currently amended) A method for treating sexual arousal disorder comprising: administering to a female subject in need thereof, an effective amount of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof and further comprising co-administering an effective amount of a cyclic guanosine 3',5'-monophosphate elevator.

47. (Previously presented) The method of claim 46 wherein the cyclic guanosine 3',5'-monophosphate elevator is a PDE_v phosphodiesterase inhibitor.

48. (Previously presented) The method of claim 47 wherein the PDE_v phosphodiesterase inhibitor is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxy-phenyl]sufonyl]-4-methylpiperazine citrate salt.

49. (canceled)

50. (Previously presented) The method of claim 45 wherein the female subject is postmenopausal.

51. (Previously presented) The method of claim 45 wherein the female subject is pre-menopausal.

52. (Currently amended) The method of claim 49 46 wherein the female subject is postmenopausal.

53. (Currently amended) The method of claim 49 46 wherein the female subject is pre-menopausal.